

48. (Amended) A method of cloning a viable animal by nuclear transfer, wherein the method is capable of introducing one or more stable genetic modifications into the cloned animal, the method comprising the steps of

- (a) obtaining a tissue sample comprising a population of NENS somatic cells as a source of nuclear donor material;
- (b) culturing the population of cells through [*a plurality of*] at least five passages so that a sufficient number of cell doublings occur to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passes;
- (c) inserting a cell from the population, or a nucleus isolated from the cell, into an enucleated oocyte from the same species to form a cybrid;
- (d) activating the cybrid;
- (e) culturing the activated cybrid until greater than a 2-cell developmental stage;
- (f) transferring the activated cybrid into an appropriate host of the same species such that the activated cybrid develops into a fetus; and
- (g) maintaining the fetus in the host until the fetus is capable of surviving and maturing into a viable animal outside of said host.

52. (Amended) The method of claim [50] 51, wherein cells from the subpopulation of cells are subject to genetic modification to produce transformed cells.

53. (Amended) [An] A non-human animal made by the method of claim 48.

54. (Amended) A non-human transgenic animal made by the method of claim 51.

56. (Amended) [An] A non-human embryo made by the method of claim 48.

57. (Amended) A non-human fetus made by the method of claim 48.

59. (Amended) A method for cloning a mammal with a cloning efficiency of better than ten percent (10%), said method comprising the steps of:

(a) inserting a somatic cell, or nucleus isolated from the somatic cell, derived from a somatic cell culture having undergone [*a plurality of*] at least five culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages, into an enucleated oocyte of the same species to form a cybrid;

(b) activating the cybrid;

- (c) culturing the activated cybrid until greater than a 2-cell developmental stage;
- (d) transferring the activated cybrid of step (c) into an appropriate host of the same species such that the activated cybrid develops into a fetus;
- (e) maintaining the fetus in the host until the fetus is capable of surviving and maturing into a viable animal outside of the host; wherein the cloning efficiency of such method is better than ten percent (10%).

60. (Amended) A method for the cloning of a male mammal, said method comprising the steps of:

- (a) inserting a male somatic cell, or nucleus isolated from the somatic cell, selected from a somatic cell culture having undergone *[a plurality of]* at least five culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages, into an enucleated oocyte to form a cybrid;
- (b) activating the cybrid;
- (c) culturing the activated cybrid until greater than a 2-cell developmental stage;
- (d) transferring the activated cybrid of step (c) into an appropriate host such that the activated cybrid develops into a fetus;

(e) maintaining the fetus in the host until the fetus is capable of surviving as a viable animal outside of said host.

64. (Amended) A method for producing an animal clone with genetically-engineered targeted genetic alterations, said method comprising the steps of:

(a) altering in a targeted manner the nuclear DNA of somatic cells to produce transformed cells;

(b) culturing the transformed cells through *[a plurality of]* at least five culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages;

(c) inserting nuclear material from the transformed cells into an enucleate oocyte from the same species as the donor cell to form a cybrid;

(d) activating the cybrid;

(e) culturing the activated cybrid until greater than a 2-cell developmental stage to form an embryo;

(f) transferring the embryo into an appropriate host such that the embryo develops into a fetus; and

(g) maintaining said fetus in said host until said fetus is capable of surviving and maturing into a viable animal outside of said host.

65. (Amended) [An] A non-human transgenic animal made by the method of claim 64.

66. An organ or tissue obtained from an animal made by the method of claim 64.

67. (Amended) [An] A non-human embryo made by the method of claim 64.

68. (Amended) A non-human fetus made by the method of claim 64.

70. (Amended) An improved method of cloning a mammal by nuclear transfer comprising:

(a) the introduction of a donor cell from the mammal, or donor cell nucleus, into an enucleated oocyte of the same species as the donor cell to form a cybrid;

(b) inserting the cybrid into the uterus of a host mother of said species so as to cause implantation of the cybrid into the uterus to form a fetus, and permitting the fetus to develop into the cloned mammal,

wherein the improvement comprises using as the donor cell, or donor cell nucleus, a somatic cell that has been cultured through *[a plurality of] at least five* culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic

modifications into the donor cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages, and wherein the donor cell, or donor cell nucleus, has been genetically transformed to comprise at least one addition, substitution or deletion of a nucleic acid or nucleic acid sequence.

71. (Amended) [An] A non-human animal made by the method of claim [69] 70.

72. (Amended) An organ or tissue obtained from an animal made by the method of claim [69] 70.

73. (Amended) [An] A non-human embryo made by the method of claim [69] 70.

74. (Amended) A non-human fetus made by the method of claim [69] 70.

75. (Amended) A cell line derived from cells obtained from an animal made by the method of claim [69] 70.

77. (Amended) An animal made by the method of claim [75] 76:

78. (Amended) An organ or tissue obtained from an animal made by the method of claim [75] 76.

79. (Amended) [An] A non-human embryo made by the method of claim [75] 76.

80. (Amended) A non-human fetus made by the method of claim [75] 76.